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Effect of octreotide on mouth-to-caecum transit time in healthy subjects and in the irritable bowel syndrome

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SUMMARY

The effect of a single subcutaneous injection of octreotide (50 μg) on mouth-to-caecum transit time was determined in patients with the irritable bowel syndrome who complained of bowel frequency, and in healthy volunteers. The assessment of mouth-to-caecum transit time was performed by monitoring breath hydrogen concentration and noting a sustained 10 p.p.m. rise after ingestion of lactulose 40 ml. Measurements were performed fasting, and on a separate day, after a standard breakfast which included 40 ml lactulose. The studies were performed double-blind in a pre-determined random order. Octreotide prolonged mouth-to-caecum transit time in irritable bowel syndrome patients and healthy subjects by factors of 2.4 and 2.6 after lactulose when fasting, respectively, and by factors of 2.8 and 2.6 after the breakfast which contained lactulose. The upper gastrointestinal transit rate was similar in irritable bowel syndrome patients and healthy controls.

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INTRODUCTION

Although the exact physiological role of somatostatin remains to be defined, intravenous administration of this hormone modulates numerous gut functions. In view of its ability to suppress gut and pancreatic functions,[1–7] and the secretion of other gastrointestinal hormones,[8,9] it has been regarded as an 'endocrine cyanide'.[10] Therapeutic uses of somatostatin have been hindered by its short circulating half-life of 1–2 min.[11] Octreotide, however, a synthetic octapeptide analogue of the naturally occurring peptide, somatostatin, has a circulating half-life of 1–2 h after subcutaneous administration,[12] and therefore has a greater therapeutic potential.

In the irritable bowel syndrome, abnormalities of smooth muscle function have been found throughout the gut.[13] Relief of irritable bowel syndrome symptoms by somatostatin,[14] and a trend towards decreased fasting concentrations of plasma somatostatin in the irritable bowel syndrome have also been reported.[15] We have therefore examined the effects of octreotide on small bowel transit time in patients with the irritable bowel syndrome and in healthy controls.

PATIENTS AND METHODS

Twelve consecutive patients (age range 18–65 years; nine women) with the irritable bowel syndrome of a duration greater than 6 months, and who complained of diarrhoea and bowel frequency (> 4 bowel actions/day), were recruited from the gastroenterology out-patient clinic. All patients fulfilled the criteria of Manning *et al.*,[16] had normal findings on physical examination, and had normal investigations including full blood count, erythrocyte sedimentation rate, serum albumin, liver biochemistry, sigmoidoscopy, rectal biopsy and, if appropriate, barium enema or colonscopy. Thirteen healthy volunteers (age range 22–36 years; four women) acted as control subjects. None of the volunteers admitted to abdominal symptoms and all had a regular bowel habit of 1–2 actions per day. Neither patients nor volunteers took medication known to affect gastrointestinal function for at least 72 h before the study. All the subjects gave informed consent and the study was approved by the Ethics Committee of the City and Hackney Health District.

Mouth-to-caecum transit time was determined by monitoring end-expiratory breath hydrogen concentrations (Hydrogen analyser, GMI Medical Ltd, Renfrew) under basal conditions following 50 ml 0.2% (w/v) chlorhexidine gluconate mouth wash and at 15-min intervals after ingestion of 40 ml lactulose. A sustained 10 p.p.m. rise in breath hydrogen concentration was regarded as indicative that the lactulose had arrived in the caecum.

After a 12-h overnight fast, mouth-to-caecum transit time was measured 'double-blind' in both irritable bowel syndrome patients and healthy volunteers after 40 ml lactulose. Thirty minutes before lactulose ingestion, subjects received in random order 50 μg octreotide (Sandoz Ltd) by subcutaneous injection or, on a separate day at least 1 week apart, placebo (octreotide diluent). In addition, using a

Table 1. Effect of a 50 μg single subcutaneous injection of octreotide on mouth-to-caecum transit time in the irritable bowel syndrome patients and normal subjects

		Mean mouth-to-caecum transit time ± s.e.m. (min)	
	n	Placebo	Octreotide
Healthy subjects (fasted)	8	87 ± 7	227 ± 7*
Irritable bowel syndrome patients (fasted)	6	75 ± 10	181 ± 14*
Healthy subjects (after meal)	7	81 ± 12	212 ± 23*
Irritable bowel syndrome patients (after meal)	7	77 ± 12	197 ± 20*

* $P < 0.001$ (paired *t*-test). *n* refers to the number of patients studied; not all patients or controls took part in both studies.

similar protocol, we studied the effect of octreotide and placebo on mouth-to-caecum transit time after a standard breakfast (two boiled eggs, 80 g toasted white bread, 10 g butter, 20 g marmalade, 50 ml sweetened orange juice, 200 ml water; 67 g carbohydrate, 20 g fat, 17 g protein) to which 40 ml lactulose was added.

RESULTS

The mouth-to-caecum transit time was similar in both the irritable bowel syndrome patients and the controls following lactulose alone, and when lactulose was taken with the standard breakfast (Table 1). Octreotide prolonged mouth-to-caecum transit time after 40 ml lactulose in all irritable bowel syndrome patients and all healthy subjects. Mean mouth-to-caecum transit times were increased by factors of 2.4 and 2.6, respectively, by octreotide in these two groups (Table 1). After the standard breakfast, octreotide also prolonged mean mouth-to-caecum transit time by factors of 2.8 and 2.6. Again, this change was observed in all subjects. There was no significant difference in the prolongation of mouth-to-caecum transit time between healthy subjects and irritable bowel syndrome patients. No side-effects were reported apart from mild discomfort at the injection site.

DISCUSSION

The results of this study demonstrate that octreotide is a potent inhibitor of upper gastrointestinal transit in both the fasted and fed state. This is true both in healthy subjects and patients with the irritable bowel syndrome. The increased mouth-to-caecum transit time in the fed state confirms previous findings in healthy volunteers, in which octreotide-induced prolongation of small intestinal transit occurred in association with a reduced nutrient absorption.[3, 17]

Other workers who used the lactulose hydrogen breath test have shown that

60 mg codeine phosphate and 12 mg loperamide increase mouth-to-caecum transit time by factors of 1.8 and 1.7, respectively, in normal subjects.[18] Octreotide appears to be more potent than these commonly used anti-diarrhoeal agents, and increases mouth-to-caecum transit time approximately 2.7-fold after a meal.

The findings of the present study indicate that mouth-to-caecum transit time is the same in healthy subjects and 'diarrhoea-predominant' irritable bowel syndrome patients. The subdivision of irritable bowel syndrome into 'diarrhoea-predominant' and 'constipation-predominant' groups, on the basis of bowel frequency,[19] may therefore be misleading as mouth-to-caecum transit time in patients with increased bowel frequency does not differ from healthy controls. This contention is supported by the finding that there is no relationship between the frequency of defaecation and whole-gut transit time in the irritable bowel syndrome.[20]

In view of its potency in inhibiting upper gastrointestinal transit, octreotide may be of therapeutic value in a number of diarrhoeal conditions. It has already been used with some success in the short bowel syndrome and post-vagotomy diarrhoea.[18, 21–23] The therapeutic use of octreotide in the irritable bowel syndrome[14] awaits further clinical investigation.

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